

REMARKS

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Claims 1-9, 39-47, and ~~48~~-61 are pending, Claims 55-61 were added.

Claims 1, 9, 41, and 45 were amended; the amendment is supported by disclosure throughout the specification, e.g., at page 13, line 29 to page 14, line 23, as well as page 14, lines 14-15, of the specification. Claim 45 was rewritten to be in independent form, incorporating the requirements of independent claim 41 from which it originally depended. New claims 55, 56, and 59 are supported by disclosure at page 2, lines 25-27, of the specification. New claim 57 is supported by disclosure at page 1, line 27, of the specification. New claims 58 and 59 are further supported by disclosure at page 14, lines 19-23, of the specification. New claims 60 and 61 are supported by disclosure at page 35, lines 11-14, of the specification.

No new matter has been added by this amendment.

35 U.S.C. § 102(b)

Claims 41, 42, 44, 48, 49, and 50 were rejected for anticipation by Lavaissiere et al.

On page 6, lines 7-13, of the Office Action, the Examiner states:

Lavaissiere et al. teaches the detection method of the antigen-antibody complex with immunohistochemical staining (claim 44) of a bodily tissue of a mammal from a biopsy of a solid tumor (claim 42), cholangiocarcinoma (claim 48 with inherently similar antibodies (claim 49 and 40) to FB-50 mAb which bind to a HAAH polypeptide to form an antigen-antibody complex. Lavaissiere et al. further teaches detection of the antigen-antibody complex occurs in the cholangiocarcinoma, but not in the normal bile ducts.

Claim 48 has been canceled. Claim 41 has been amended to require that the malignant neoplasm be a neoplasm of the central nervous system (CNS). Lavaissiere et al. fail to describe or suggest diagnosis of CNS tumors. Therefore, this rejection should be withdrawn.

35 U.S.C. § 112, first paragraph

Claims 1-9, 39, 40, 43, 45, 46, 51, and 52 were rejected for lack of enablement. On page 4, lines 2-9 of the Office Action, the Examiner stated:

The most urgent issues that the specification has not taught in order to use the instant invention for the purposes stated in the preamble are; (1) does a bodily fluid of a mammal that has a malignant neoplasm contain HAAH polypeptide? If it exists, (2) does the polypeptide in the *bodily fluid* and *tissue samples* exist as a same form or in a different splicing variant or other modified form to overcome the solubility problem in a bodily fluid? If two different forms exist, then (3) is it possible to use the monoclonal antibody in claims 6-8 to detect the form in a bodily fluid....No evidence exists that HAAH could be detected using the method described on page 14, claims 1-9, and 39, 40, 43, 45, 46, 51, and 52. (emphasis in the original).

The Examiner appears to be concerned about a lack of a working example showing a correlation between HAAH in a bodily fluid and a malignancy, citing to an abstract by Weg-Remers et al. The Weg-Remers et al. abstract reports overexpression of CD44 variants in serum and tissue samples of tumor patients, concluding that levels of the soluble forms of CD44 showed no correlation to tumor burden.

Contrary to the observations of Weg-Remers, an increase in HAAH level in both bodily fluid samples and tissue samples ^{not issue} correlate with a diagnosis of malignancy. Applicants have now tested both tissue samples and bodily fluid samples obtained from normal control subjects and cancer patients using the methods described on pages 14-15 of the specification. The Declaration of Michael S. Lebowitz describes HAAH detection in bodily fluids. Bodily fluid samples were collected from normal (no known cancer) individuals as well as individuals, who had been previously diagnosed with malignant breast or prostate cancer. Detection of HAAH was carried out using a standard antibody-binding assay (sandwich ELISA) and HAAH-specific antibodies, FB50 and 5C7. The data indicate that an increase in the level of HAAH polypeptide

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in a human bodily fluid as measured using an HAAH-specific antibody correlates with a diagnosis of cancer, i.e., the presence of a malignant neoplasm.

In view of the direction provided in the specification regarding how to measure HAAH levels in human bodily tissues (bodily fluids as well as solid tissue) and the data confirming the correlation between increased HAAH levels in bodily fluid and malignancy, Applicants submit that the claims fulfill the requirements of 35 U.S.C. § 112.

Claims 41, 42, 44, 47, 49, 50, 53, 54 were also rejected for lack of enablement. These claims are drawn to methods diagnosing malignant neoplasms by detecting HAAH levels in bodily tissues. The Examiner alleges that undue experimentation would be required to practice the claims. On page 4, lines 20-24, the Examiner states:

Claims 41, 42, 44, 47, 49, 50, 53, 54 say detecting a HAAH polypeptide antigen-antibody complex in a bodily tissue is sufficient to diagnosis of a malignant tumor but Lavaissiere et al.(Table 1) says that the antigen is also present in some normal tissues, especially liver. Therefore, detection of the antigen is not sufficient to diagnosis of cancer.

This rejection is traversed. The diagnostic method claimed requires an increased level of HAAH in a test sample compared to a normal noncancerous control sample for a diagnosis of cancer. Although Lavaissiere et al. report detection of HAAH in some normal tissues, the level of expression was low (“low level of expression in normal hepatocytes and in non-neoplastic epithelial cells”; see Abstract of Lavaissiere et al.). These researchers also state “Among the normal adult tissues studied, high levels were observed only in proliferating trophoblast cells of the placenta and in adrenal glands.” (Abstract of Lavaissiere et al.). This reference does not suggest that detection of an increased level of HAAH (as is required by the claims) is not sufficient to diagnose cancer.

Claim 41 has now been amended to require CNS cancers. The data described in Example 2 (pages 35-45 of the specification) provide evidence that HAAH is increased in malignant CNS neoplasms (compared to normal noncancerous controls). The declaration of Michael J. Lebowitz (see Table 2 of the Declaration) provides additional evidence that HAAH is increased in CNS cancers such as glioblastoma, oligodendroglioma, and neuroectodermal tumors (as well as other malignant tumors) compared to normal noncancerous tissue samples. These data indicate the reliability and predictability of the claimed diagnostic method.

Applicants submit that the amended claims meet the requirements of § 112 of the patent statute because (1) the Lavaissiere et al. reference fails to suggest that undue experimentation would be required to practice the claimed invention, (2) the specification provides extensive guidance regarding how to measure HAAH levels in tissue samples, and (3) the accompanying Declaration of Michael J. Lebowitz provide additional evidence of the correlation between increased HAAH levels in various malignant tissues compared to normal non-cancerous tissues. This rejection should therefore be withdrawn.

35 U.S.C. §112, second paragraph

Claims 1-8, 39, 40, 43, 46, 51, and 52 were rejected as being incomplete for omitting determination steps to achieve the purpose stated in the preamble. The claims have been amended to address the Examiner's objection.

Claims 41, 42, 44, 47-50, 53, and 54 were also rejected as being incomplete for omitting determination steps to achieve the purpose stated in the preamble. The Examiner states that the claims need "relating step steps linking the detection of antigen-antibody complex to diagnosing a malignant neoplasm". The claims have been amended to add the relating step suggested by the Examiner.

With respect to claims 1, 9, and 41, the Examiner objected to the claim language “under conditions sufficient to form an antigen-antibody complex”, stating that “it is unclear what the metes and bounds are....” Applicants submit that conditions for antigen-antibody complex formation are well known in the art, i.e., there would be no ambiguity regarding the meaning of the phrase to one skilled in the art of immunochemistry and clinical diagnostics. Moreover, the antigen-antibody detection assays are fully described on pages 14-15 of the specification. The assays and the conditions under which the assays are carried out have been known in the art for decades. Therefore, Applicants request that this rejection be withdrawn.

The Examiner objected to the claim term “a normal control level” in claim 9. Applicants have amended claim 9 (as well as other applicable claims) to require a normal –noncancerous— control. Applicants believe that this amendment meets the rejection, and therefore request withdrawal of this rejection.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance.

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Applicants file concurrently herewith a petition for a two (3) month extension of time, together with a check for \$460.00 to cover the fee pursuant to 37 C.F.R. § 1.17(a)(3). With the extension, this amendment is due on or before July 19, 2001. The Commissioner is hereby authorized to charge same, or credit any overpayment, to Deposit Account No. 50-0311 (Reference No. 21486-032).

Respectfully submitted,



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EXHIBIT A

Marked up Version

In the claims:

Cancel claim 28 and 48. Amend claims 1, 9, 41 and 45. Add new claims 55-61.

1. (amended) A method for diagnosing a malignant neoplasm in a mammal, comprising contacting a bodily fluid from said mammal with an antibody or fragment thereof which binds to an human aspartyl (asparaginy) beta-hydroxylase (HAAH) polypeptide under conditions sufficient to form an antigen-antibody complex and detecting the antigen-antibody complex, wherein an increase in antigen-antibody complex indicates an increase in HAAH level compared to a normal noncancerous control, said increase being indicative of a malignant neoplasm.

9. (amended) A method for prognosis of a malignant neoplasm of a mammal, comprising

(a) contacting a bodily fluid from said mammal with an antibody which binds to an HAAH polypeptide under conditions sufficient to form an antigen-antibody complex and detecting the antigen-antibody complex;

(b) quantitating the amount of complex to determine the level of HAAH in said fluid; and

(c) comparing the level of HAAH in said fluid with a normal noncancerous control level of HAAH, wherein increasing levels of HAAH over time indicates an adverse prognosis.

41. (amended) A method of diagnosing a malignant neoplasm of the central nervous system in a mammal, comprising contacting a bodily tissue from said mammal with an antibody or fragment

thereof which binds to a HAAH polypeptide under conditions sufficient to form an antigen-antibody complex and detecting the antigen-antibody complex, wherein an increase in antigen-antibody complex indicates an increase in HAAH level compared to a normal noncancerous control, said increase being indicative of a malignant neoplasm.

45. (amended) [The method of claim 1,] A method of diagnosing a malignant neoplasm in a mammal, comprising contacting a bodily tissue from said mammal with an antibody or fragment thereof which binds to a HAAH polypeptide under conditions sufficient to form an antigen-antibody complex and detecting the antigen-antibody complex, wherein an increase in HAAH compared to a normal control indicates the presence of a malignant neoplasm and wherein said neoplasm is a hepatocellular carcinoma.

55. (new) A method of diagnosing a malignant neoplasm in a mammal, comprising contacting a bodily tissue from said mammal with an antibody or fragment thereof which binds to a HAAH polypeptide under conditions sufficient to form an antigen-antibody complex and detecting the antigen-antibody complex, wherein said antibody is selected from the group consisting of 5C7, 5E9, 19B, 48A, 74A, 78A, 86A, HA238A, HA221, HA 239, HA241, HA329, or HA355 and wherein an increase in HAAH compared to a normal control indicates the presence of a malignant neoplasm.

56. (new) The method claim 51, wherein said antibody is 5C7.

57. (new) A method of diagnosing a malignant neoplasm in a mammal, comprising contacting a bodily tissue from said mammal with an antibody or fragment thereof which binds to a HAAH

polypeptide under conditions sufficient to form an antigen-antibody complex and detecting the antigen-antibody complex, wherein an increase in HAAH compared to a normal control indicates the presence of a malignant neoplasm and wherein said neoplasm is a pancreatic cancer.

58. (new) The method of claim 1, wherein said antibody comprises a first HAAH-specific antibody and a second HAAH-specific antibody.

59. (new) The method of claim 58, wherein said first antibody and said second antibody are selected from the group consisting of FB50 and 5C7.

60. (new) The method of claim 41, wherein said neoplasm is an oligodendroglioma.

61. (new) The method of claim 41, wherein said tumor is a neuroectodermal tumor.